Original Investigation | META-ANALYSIS

Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk
A Meta-analytical Stratification

Paolo Fusar-Poli, MD, PhD; Marco Cappucciati, MD; Stefan Borgwardt, MD, PhD; Scott W. Woods, MD; Jean Addington, PhD; Barnaby Nelson, PhD; Dorien H. Nieman, PhD; Daniel R. Stahl, PhD; Grazia Rutigliano, MD; Anita Riecher-Rössler, MD, PhD; Andor E. Simon, MD; Masafumi Mizuno, MD, PhD; Tae Young Lee, MD; Jun Soo Kwon, MD, PhD; May M. L. Lam, MBBS; Jesus Perez, PhD; Szabolcs Keri, MD, PhD; Paul Amminger, MD, PhD, FRANZCP; Sibylle Metzler, PhD; Wolfram Kawohl, MD; Wulf Rössler, MSc, MD; Jimmy Lee, MBBS, MMed(Psychiatry), MCI; Javier Labad, MD, PhD; Tim Ziermans, PhD; Suk Kyoon An, MD, PhD; Chen-Chung Liu, MD, PhD; Kristen A. Woodberry, MSW, PhD; Amel Braham, MD; Cheryl Corcoran, MD; Patrick McGorry, MD, PhD, FRCP, FRANZCP; Alison R. Yung, MD; Philip K. McGuire, MD, PhD

IMPORTANCE Individuals can be classified as being at clinical high risk (CHR) for psychosis if they meet at least one of the ultra–high-risk (UHR) inclusion criteria (brief limited intermittent psychotic symptoms [BLIPS] and/or attenuated psychotic symptoms [APS] and/or genetic risk and deterioration syndrome [GRD]) and/or basic symptoms [BS]. The meta-analytical risk of psychosis of these different subgroups is still unknown.

OBJECTIVE To compare the risk of psychosis in CHR individuals who met at least one of the major inclusion criteria and in individuals not at CHR for psychosis (CHR−).

DATA SOURCES Electronic databases (Web of Science, MEDLINE, Scopus) were searched until June 18, 2015, along with investigation of citations of previous publications and a manual search of the reference lists of retrieved articles.

STUDY SELECTION We included original follow-up studies of CHR individuals who reported the risk of psychosis classified according to the presence of any BLIPS, APS and GRD, APS alone, GRD alone, BS, and CHR−.

DATA EXTRACTION AND SYNTHESIS Independent extraction by multiple observers and random-effects meta-analysis of proportions. Moderators were tested with meta-regression analyses (Bonferroni corrected). Heterogeneity was assessed with the I^2 index. Sensitivity analyses tested robustness of results. Publication biases were assessed with funnel plots and the Egger test.

MAIN OUTCOMES AND MEASURES The proportion of each subgroup with any psychotic disorder at 6, 12, 24, 36, and 48 or more months of follow-up.

RESULTS Thirty-three independent studies comprising up to 4227 individuals were included. The meta-analytical proportion of individuals meeting each UHR subgroup at intake was: 0.85 APS (95%CI, 0.79-0.90), 0.1 BLIPS (95%CI, 0.06-0.14), and 0.05 GRD (95%CI, 0.03-0.07). There were no significant differences in psychosis risk at any time point between the APS and GRD and the APS-alone subgroups. There was a higher risk of psychosis in the any BLIPS greater than APS greater than GRD-alone subgroups at 24, 36, and 48 or more months of follow-up. There was no evidence that the GRD subgroup has a higher risk of psychosis than the CHR− subgroup. There were too few BS or BS and UHR studies to allow robust conclusions.

CONCLUSIONS AND RELEVANCE There is meta-analytical evidence that BLIPS represents separate risk subgroup compared with the APS. The GRD subgroup is infrequent and not associated with an increased risk of psychosis. Future studies are advised to stratify their findings across these different subgroups. The CHR guidelines should be updated to reflect these differences.

JAMA Psychiatry. 2016;73(2):113-120. doi:10.1001/jamapsychiatry.2015.2324
Published online December 30, 2015.

Editorial page 105

Supplemental content at jamapsychiatry.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Paolo Fusar-Poli, MD, PhD, Institute of Psychiatry, Psychology, and Neuroscience, King's College, PO Box 63, De Crespigny Park, SE58AF London, United Kingdom (paolo.fusar-poli@kcl.ac.uk).

The first clinical service for individuals potentially prodromal for psychosis (Personal Assessment and Crisis Evaluation Clinic) was set up in 1995 by Yung et al[1] in Melbourne, Australia, on the basis of the ultra-high-risk (UHR) criteria. Inclusion required the presence of one or more of the following: attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), and/or genetic risk and deterioration (GRD) criteria (for historical details, see the article by Fusar-Poli et al[2]). These subgroups were defined a priori as independent entry criteria, and they are independently operationalized on the psychometric assessment tools that are used to ascertain the UHR state. Adolescents and young adults at increased risk of developing psychotic disorders can thus be identified using standardized psychometric instruments with consistent reliability and good predictive value.[3] The risk of psychosis in UHR individuals peaks during the ensuing 2 years.[4] However, despite a great deal of research for reliable clinical, behavioral, or neurobiological measures that can predict the subsequent onset of psychosis, researchers have yet to discover such a holy grail.[5]

The lack of reliable and valid predictive biomarkers[6] may reflect a number of factors, including the declining transition risks in recent years,[7,8] small sample sizes, a lack of external validation,[6] and methodologic pitfalls.[9] However, a key potential confounder is that the UHR category may itself be heterogeneous.[10] When the UHR paradigm was devised, the founders suggested that there may be different UHR subgroups, each associated with different levels of risk. In particular, it was hypothesized that the group with the presence of any BLIPS (ie, BLIPS alone, BLIPS and APS, or BLIPS and APS and GRD) would have the highest level of risk, followed by the group with APS and GRD (additive clinical and genetic effect on psychosis risk), the group with APS alone, and then the GRD-alone group.[11] However, to our knowledge, this assumption has not previously been systematically tested using a meta-analytical approach. A further complication is that a comparably high risk of psychosis has been independently associated with the basic symptoms (BS) criteria,[12] which are thought to represent another separate and different subgroup, featuring an earlier phase of prodromal psychosis than the UHR criteria.[2] Many high-risk centers now include individuals with UHR and/or BS in their studies, and this combination can be termed as defining a clinical high-risk (CHR) state for psychosis. The extent to which all these different subgroups can be considered as belonging to a single CHR group is unclear. However, if the CHR category is heterogeneous, this may hamper ongoing efforts to understand the mechanisms underlying the risk of psychosis and the development of preventive treatments.

In the present study, we investigated this issue by conducting, to our knowledge, the first robust meta-analytical investigation of risk stratification across different CHR subgroups. We test the hypothesis of heterogeneous risk levels in UHR, stratified as any BLIPS greater than APS and GRD, greater than APS, alone greater than GRD alone.[11] To test the actual risk of psychosis, these subgroups are additionally compared with individuals assessed for suspicion of psychosis risk but not meeting CHR criteria (hereafter CHR−). This analysis is complemented by meta-regressions, investigating the effect of potential confounders on the meta-analytical estimates, and by secondary analyses on BS subgroups.

Methods

Search Strategy

Two investigators (M.C., G.R.) conducted 2-step literature searches. First, the Web of Knowledge database was searched, incorporating both the Web of Science and MEDLINE. The search was extended until June 18, 2015, including abstracts in the English language only. The electronic research used several combinations of the following keywords: *at risk mental state*, *psychosis risk*, *prodrome*, *prodromal psychosis*, *ultra high risk*, *high risk*, *help seeking patients*, *psychosis prediction*, *psychosis onset*, and the names of the diverse CHR assessment instruments. Second, Scopus was used to investigate citations of possible previous reviews and meta-analyses on transition to psychosis in CHR individuals and a manual search of the reference lists of retrieved articles. Articles identified through these 2 steps were then screened in relation to the selection criteria on the basis of reading their abstracts. Discrepancies were discussed with another author (P.F.-P.) and resolved through consensus. The articles surviving this selection were assessed for eligibility on the basis of full-text reading, following the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) checklist (eTable 1 in the Supplement).[13]

Selection Criteria

Studies were eligible for inclusion when the following criteria were fulfilled: (1) an original article, written in English; (2) inclusion of CHR individuals, defined according to established international UHR criteria (ie, Comprehensive Assessment of at Risk Mental States, Structured Interview for Psychosis-Risk Syndromes, Basel Screening Instrument for Psychosis) and/or BS criteria (Schizophrenia Proneness Instruments, Bonn Scale for the Assessment of Basic Symptoms) instruments[14-19] or CHR− individuals; (3) prospective assessment of risk of psychosis onset with at least one follow-up time point (6, 12, 24, 36, and/or ≥48 months); (4) reported risk of psychosis stratified across the following CHR subgroups: any BLIPS, APS and GRD, APS alone, GRD alone (individuals meeting multiple UHR criteria were stratified for symptom severity as previously suggested: any BLIPS greater than APS and GRD, greater than APS alone, greater than GRD alone[11]), BS, and/or across the CHR− subgroup. CHR− individuals were defined as help-seeking individuals referred to ultra-high-risk services (UHR) and/or to expert clinicians (BS) for suspicion of psychosis risk and assessed with the standardized CHR instruments but not meeting CHR criteria. This comparison group was thus drawn from the same pool of referrals that provided the individuals who met the CHR criteria.

When studies had not already subdivided the CHR sample and assessed risk of psychosis in each subgroup, the corresponding author was contacted and invited to use the original raw data to stratify the samples. A similar approach was adopted with respect to collection of potential moderators for

each subgroup. Exclusion criteria were (1) abstracts, pilot data sets, and articles in languages other than English; (2) articles that did not use internationally validated definitions for CHR (ie, UHR and/or BS); (3) articles with overlapping data sets; and (4) studies that could not provide data on transition risk in relation to these subgroups. In the case of multiple publications deriving from the same study population, we selected the articles that reported the longest follow-up data set. The literature search was summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[20]

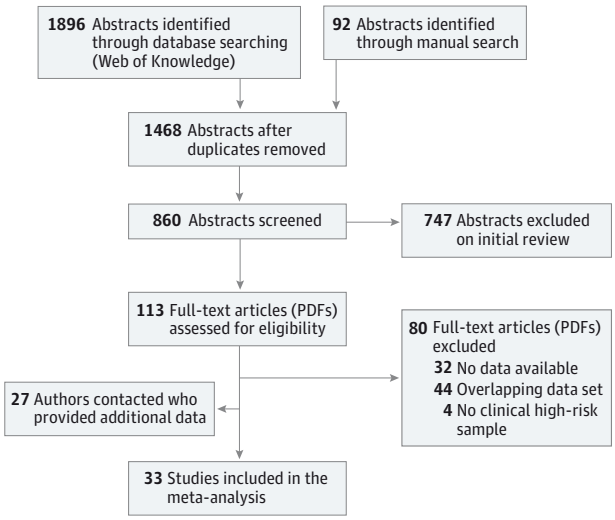
Recorded Variables

Data extraction was independently performed by 2 investigators (M.C., G.R.). To estimate the primary outcome variable, we extracted the baseline sample size and the number of individuals with psychosis at each follow-up time point across each UHR subgroup. To estimate the secondary outcome, we further collected number of transitions across the UHR only, BS only, and BS and UHR subgroups. Additional moderators tested in meta-regression analyses are listed in the statistical analysis below. Quality assessment is described in the eMethods in the Supplement.

Statistical Analysis

The primary outcome was the risk of psychosis onset in CHR individuals, stratified according to the initial UHR subgroups, with the following order: any BLIPS greater than APS and GRD, greater than APS alone, greater than GRD alone, greater than CHR−. This was calculated as the proportion of baseline individuals across each subgroup with any psychotic diagnosis at 6, 12, 24, 36, and 48 or more months of follow-up. The baseline sample size was conservatively used to avoid a bias toward overly high transition risks at longer follow-ups resulting from an increase of dropouts over time. In case of a lack of meta-analytical differences between the APS alone and APS and GRD subgroups, it was planned a priori to repeat the analyses with these 2 subgroups combined in a single group (ie, BLIPS greater than APS, greater than GRD, greater than CHR−[11]). The meta-analysis was conducted with the metaprop package[21] of STATA statistical software, version 13.1 (StataCorp), which has been specifically developed for pooling proportions in a meta-analysis of multiple studies. The 95% CIs were based on score (Wilson) procedures.[22] Because proportions were often expected to be small, we used Freeman-Tukey Double Arcsine transformation[23] to stabilize the variances and then perform a random-effects meta-analysis implementing the DerSimonian-Laird method.[24] The influence of moderators was tested using meta-regression analyses with the metareg function,[25] and the metareg permutation test option was used to estimate the 95% CIs. The slope of the meta-regression line (β-coefficient: direct or inverse) indicates the strength of an association between moderator and outcome. The meta-regressions were conducted when at least 10 studies were available for each moderator[26] and were Bonferroni corrected for multiple testing. Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index,[27] which does not depend on the number of studies included. Because meta-analyses of observational studies are expected to be characterized by significant heterogeneity, random-effects models were used. In addition, we conducted sensitivity analyses to investigate the influence of each single study on the overall risk estimate by omitting one study at a time, using Stata's user-written function metainf.[28,29] A study was considered to be influential if the pooled mean estimate without it was not within the 95% CI of the overall mean. Publication biases were assessed with the metafunnel function of Stata that produced funnel plots for assessing small-study reporting bias in meta-analysis[30] and with the Egger test[31] in metabias[32] function of Stata. We investigated as secondary outcomes the risk of psychosis in individuals who met the original UHR criteria only, in individuals who met the BS criteria only, and in individuals who met both the BS and UHR criteria.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Diagram



Results

Database

The literature search (**Figure 1**) identified 33 independent articles, most of which contributed more than one UHR or BS subgroup. The details of the included studies and types of samples provided are detailed in eTable 2 in the Supplement. The age and sex of the CHR samples, psychometric CHR instruments, diagnostic instrument used to assign the psychotic diagnosis, duration of follow-up, and exposure to antipsychotics at baseline and baseline to follow-up, quality assessment, and baseline sample sizes of the CHR and CHR− patient subgroups are detailed in eTable 2 in the Supplement.

The overall characteristics of the UHR samples are detailed in the eResults in the Supplement. Across the studies using the UHR criteria (n = 3624), the baseline meta-analytical proportion of individuals meeting the 3 subgroups was as follows:

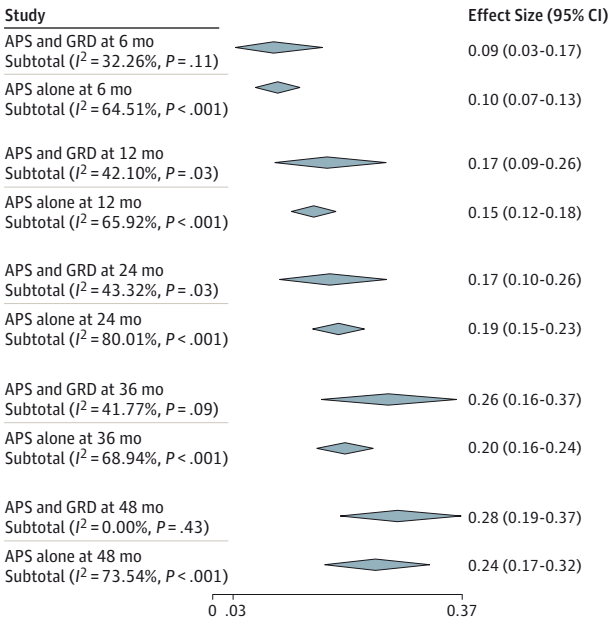
APS, 0.85 (95% CI, 0.79-0.90); BLIPS, 0.10 (95% CI, 0.06-0.14); and GRD, 0.05 (95% CI, 0.03-0.07) (eFigure 1A, B, and C in the Supplement) (individuals who met multiple intake criteria were categorized as planned: BLIPS greater than APS, greater than GRD[11]).

Meta-analytical Stratification of Individuals at Ultra–High-Risk for Psychosis

There were no significant meta-analytical differences between the APS and GRD and the APS-alone subgroups at any time point (**Figure 2**). We therefore combined these 2 subgroups into a single APS subgroup and contrasted it with the BLIPS and GRD subgroups (BLIPS greater than APS, greater than GRD[11]).

The 33 independent studies reported primary outcome data at a variety of different follow-up time points, with an overall sample size of up to 4227 participants (**Figure 3** and **Table**). There was meta-analytical evidence of higher risk of psychosis in the BLIPS greater than APS, greater than GRD after 24 months of follow-up, but this effect was not evident at 6 or 12 months. Across the BLIPS and APS subgroups, the psychosis risk peaked at 24 months and then plateaued. There was no meta-analytical evidence that the GRD subgroup had higher risk of psychosis than the CHR– subgroup at any time point.

Figure 2. Risk of Psychosis Over Time in the Attenuated Psychotic Symptoms (APS) and Genetic Risk and Deterioration Syndrome (GRD) vs APS-Alone Groups



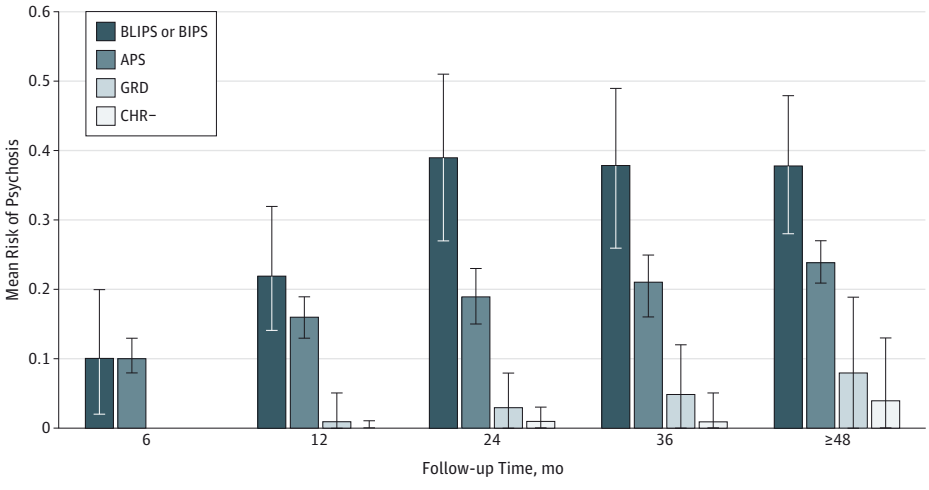
Test for between-group heterogeneity (P > .05 at all time points).

Sensitivity Analyses, Publication Biases, and Meta-regressions

Meta-regressions that investigated year of publication, mean age of subgroup, proportion of females in each UHR subgroup, baseline functional level in each subgroup, duration of untreated attenuated psychotic symptoms, exposure to antipsychotics from baseline to follow-up, psychometric UHR criteria, diagnostic criteria used to assess transition to psychosis at follow-up, and quality assessment are appended in eTable 3 in the Supplement. There was a significant effect for publication year on risk of psychosis onset at 24 months, with the most recent studies reporting a lower risk than the oldest studies (eFigure 2A in the Supplement). A higher proportion of antipsychotic agent exposure was associated with an increased risk of psychosis at 36 months (eFigure 2B in the Supplement). All the other meta-regressions did not produce significant effects.

Sensitivity analyses (results available from the authors on request) confirmed the robustness of the results at all time points. Removal of an outlier identified at 12, 24, or 36 months[33] did not alter the main findings of significant between-groups heterogeneity (P < .001). There was no evidence of publication biases as indicated by visual inspections of the funnel plots and by the Egger test for small study effects (eFigure 3A-E in the Supplement).

Figure 3. Meta-analytical Stratification of Ultra–High-Risk Individuals



APS indicates attenuated psychosis symptoms; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; GRD, genetic risk and deterioration syndrome; CHR–, not at clinical high risk for psychosis. Error bars indicate 95% CI.

Table. Risk of Psychosis Across Ultra–High-Risk Subgroups

Follow-up Time, mo	BLIPS/BIPS	APS	GRD	CHR−	Total Sample	Test for Between-Group Heterogeneity (Q)	*P* Value
6							
No. of studies (No. of individuals)	19 (219)	19 (1839)	19 (154)	8 (1021)	65 (3233)	119.32	<.001
Mean (95% CI)	0.10 (0.02-0.20)	0.10 (0.08-0.13	0 (0-0.01)	0 (0-0.02)			
12							
No. of studies (No. of individuals)	24 (294)	24 (2093)	24 (161)	7 (879)	79 (3472)	145.65	<.001
Mean (95% CI)	0.22 (0.14-0.32)	0.16 (0.13-0.19)	0.01 (0-0.05)	0 (0-0.01)			
24							
No. of studies (No. of individuals)	22 (285)	22 (2694)	22 (196)	8 (1052)	74 (4227)	124.31	<.001
Mean (95% CI)	0.39 (0.7-0.51)	0.19 (0.15-0.23)	0.03 (0-0.08)	0.01 (0-0.03)			
36							
No. of studies (No. of individuals)	12 (180)	12 (1533)	12 (122)	7 (863)	43 (2698)	62.13	<.001
Mean (95% CI)	0.38 (0.26-0.49)	0.21 (0.16-0.25)	0.05 (0-0.12)	0.01 (0-0.05)			
≥48							
No. of studies (No. of individuals)	6 (137)	6 (734)	6 (64)	3 (134)	21 (1069)	32.75	<.001
Mean (95% CI)	0.38 (0.28-0.48)	0.24 (0.21-0.27)	0.08 (0-0.19)	0.04 (0-0.13)			

Abbreviations: APS, attenuated psychotic symptoms; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; GRD, genetic risk and deterioration syndrome; CHR−, help-seeking individuals not at clinical high risk for psychosis.

Secondary Outcomes

The secondary analyses (UHR alone vs BS alone vs UHR and BS) revealed that, compared with the UHR criteria alone, there was a higher psychosis risk in the UHR and BS subgroup at 36 months and in the UHR and BS, and BS-alone subgroups at 48 months (eFigure 4 and eTable 4 in the Supplement). However, these results should be considered exploratory because there were only very few individual studies included.

Discussion

The current study provided, to our knowledge, the first robust meta-analytical support for the existence of heterogeneous subgroups within the CHR samples. Most of the UHR individuals were included at intake because of APS (85%), with BLIPS (10%) and GRD (5%) less frequent (eDiscussion 1 in the Supplement). The meta-analysis indicated that these subgroups differed according to the level of risk, with BLIPS having a higher transition risk than APS, and APS having a higher transition than GRD. There was no evidence of enhanced risk in the GRD subgroup compared with the CHR− subgroup.

We found no evidence supporting additive risk for comorbid APS and GRD, operationalized as independent constructs in the psychometric interviews, compared with APS alone (Figure 2), suggesting that it is the presence of APS that increases psychosis risk. We therefore combined these two subgroups to form a joint APS subgroup for the analyses. The results supported our main hypothesis: there was substantial between-group (BLIPS vs APS vs GRD vs CHR−) meta-analytical heterogeneity across all time points (Figure 3). Post hoc analyses revealed that this was due to a significantly higher transition risk in the BLIPS subgroup compared with the other 2 UHR subgroups (eg, 39% vs 19% in the APS at 24 months) and with the CHR− subgroup. This was evident at 24-month follow-up and remained significant in the longer term. Significant differences may not have been evident at 6 and 12 months because the proportion of transitions to psychosis at these time points was smaller than at 24 months.[4]

The inclusion of the BLIPS subgroup in the CHR has always been problematic because its diagnostic significance is unclear[34] as it overlays with the established *DSM/ICD* categories of brief psychotic disorders. Indeed, some authors have acknowledged that "patients whose fully psychotic experience is of sufficient short duration to meet *DSM* criteria for brief psychotic disorder could potentially meet prodromal criteria."[35(p 707)] Competing availability of concurrent high risk (ie, BLIPS or Brief Intermittent Psychotic Symptoms [BIPS]) and established psychosis labels of similar diagnostic significance (eg, Acute and Transient Psychotic Disorder or Brief Psychotic Disorder) may be a major source of diagnostic confusion,[36] with consequent use of arbitrary psychosis thresholds in the field.[37,38] Whether the BLIPS should be considered a feature of a high-risk state or an established psychotic disorder has been addressed in a separate study.[38] Our meta-analysis clearly reveals that the BLIP subgroup has a distinctive prognosis (with higher risk of psychosis) compared with the APS subgroup. Our finding concurs with the distinctive baseline psychopathological presentation[2] and therapeutic needs[39] as external validators of BLIPS as a separate clinical entity from APS.

This finding has a number of potential implications. For example, it may be possible for future CHR studies to limit the recruitment to the APS subgroup to reduce sample heterogeneity across subgroups,[40] which might otherwise confound the assessment of genetic, demographic, and cognitive features and neurobiological measures, as well as clinical outcomes. To date,

there have been relatively few attempts to compare the features of subgroups within CHR samples because this requires large samples. This issue can be addressed in multicenter studies. However, another possibility would be to retain the BLIPS in the CHR paradigm but as a distinct and separate subgroup to facilitate prediction of persisting psychotic disorders[38]. In addition, data from our meta-analysis may be useful for future designation of CHR programs. Health care professionals may be able to inform patients and caregivers about relative risks at a particular time point given their initial intake criteria. Interventions may thus be tailored to the different subgroups according to their prognosis. With our meta-analysis available, it is also arguable that training manuals and psychometric assessments for CHR individuals be updated to explicitly acknowledge the heterogeneity of risk levels associated with an initial CHR diagnosis.

Post hoc analyses revealed no statistically significant differences between the GRD and the CHR– subgroups (Table and Figure 3). This finding raises important concerns regarding the validity of the GRD subgroup as a true clinical high-risk syndrome, in particular given the lack of additive value for the APS designation (Figure 2) and concurrent lack of epidemiologic validation of this subgroup (prevalence for the APS and BLIPS subgroups, but not GRD, has been reported in the general population[41]). Our meta-analysis suggests that the GRD construct may not qualify as a state risk criterion[42] in that it was not associated with an impending risk for psychosis in the short term (ie, in the first 4 years). However, we cannot exclude the possibility that GRD is associated with an increased risk of psychosis during longer intervals,[42] particularly because a recent meta-analysis suggested that the impact of familial risk was only evident after the age of 20 years,[43] which was similar to the mean age in our GRD subgroup. Interpreting negative results is complex because absence of evidence is not evidence of absence[44] and because post hoc retrospective power analyses are not recommended.[45-47] The meta-analytical estimates for the GRD subgroup were based on a small sample (n < 200) and thus yielded a large CI (Figure 3). On the other hand, similar widths of CIs (and similar samples of <200 at 36 and ≥48 months) were observed in the BLIPS subgroup (Figure 3), for which significant meta-analytical differences were found. It is also possible that the decrease in function criterion required for the GRD syndrome is too low or that the instruments used to assess functional deterioration may not be the most suitable. The GRD subgroup is also heterogeneous itself, including individuals with schizotypal personality disorders and functional decline in addition to familial risk for psychosis. The risk of psychosis in people with a schizotypal personality disorder is unclear.[42] An earlier study[48] in 100 CHR individuals found that schizotypal personality disorder was infrequent and did not predict conversion. GRD may be more useful as a distal marker. In the long term (eg, after 5 years), state markers may be traded for trait markers, and thus GRD may reveal better predictive value during longer intervals.[42] Given that assessing each UHR entry criterion is demanding and challenging for clinicians and patients, additional research is urgently required to ascertain the actual clinical benefit of evaluating GRD features during CHR psychometric interviews.

We additionally tested, for the first time to our knowledge, the specific effect of several moderators of psychosis risk across each UHR subgroup (eTable 3 in the Supplement). Sex, quality of studies, type of UHR criteria, and diagnostic criteria used to assess transition to psychosis did not affect the level of risk. We also tested for the first time, to our knowledge, via meta-analytical analyses the potential impact of duration of untreated attenuated psychotic symptoms before contact with high-risk services,[8,49] finding no effect on risk of psychosis. Level of functioning at baseline similarly had no impact on risk, in contrast with data from the longest follow-up study[8] in CHR individuals and a recent meta-analysis[50] addressing functional status in CHR patients. There was also no effect for age, in contrast with our previous meta-analysis.[7] These negative findings may be secondary to lower statistical power of meta-regressions and limited variability of moderators included in the current data set, which was stratified for different subgroups. However, we did confirm the decreasing transition risk in the most recent years (eFigure 2A in the Supplement), as previously described in original studies[51,52] and meta-analytical investigations.[7,53] We also found that increased exposure to antipsychotic treatments was associated with a higher risk of psychosis (eFigure 2B in the Supplement). Such an effect may be confounded by an increase of symptoms severity, as previously observed in naturalistic studies of CHR samples[39,54] and in a meta-analysis of randomized clinical trials.[55]

Overall, this is the first robust meta-analysis to indicate that the CHR state comprises subgroups with heterogeneous levels of psychosis risk. Our meta-analysis overcomes the limitations of a previous pilot attempt[56] (eDiscussion 2 in the Supplement) by following the standard recommended guidelines and involving data from studies across the globe (Europe, United States, Asia, Africa, and Australia), with most studies providing access to additional data as necessary (27 authors sent additional meta-analytical data).

However, because of limited statistical power associated with the small number of BS studies, we were unable to provide conclusive estimates of psychosis risk in this subgroup. Because the total number of transitions was limited, we were similarly unable to differentiate the risk of transition toward schizophrenia spectrum or affective psychotic disorders.[57] We were also unable to test additional moderators potentially addressing the observed heterogeneity, such as treatments other than antipsychotics, ethnicity,[58] substance abuse,[59] and comorbid affective disorders,[53,60] because these factors had not been assessed in the original studies or were infrequent.

Conclusions

There is meta-analytical evidence of heterogeneous levels of risk of psychosis in CHR samples. The risk in the BLIPS subgroup is higher than in the APS subgroup. The GRD subgroup is rare and not associated with an increased risk of psychosis. Authors of future CHR studies are advised to stratify their findings across these different subgroups.

ARTICLE INFORMATION

Submitted for Publication: July 19, 2015; final revision received September 21, 2013; accepted September 23, 2013.

Published Online: December 30, 2015. doi:10.1001/jamapsychiatry.2015.2324.

Author Affiliations: Institute of Psychiatry, Psychology, and Neuroscience, King's College, London, United Kingdom (Fusar-Poli, Cappucciati, Stahl, Rutigliano, McGuire); OASIS Clinic, South London and Maudsley National Health Service Foundation Trust, London, United Kingdom (Fusar-Poli); Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy (Cappucciati); University of Basel Psychiatric Clinics, Basel, Switzerland (Borgwardt, Riecher-Rössler, Simon); Department of Psychiatry, Yale University, New Haven, Connecticut (Woods); Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada (Addington); Orygen, the National Centre of Excellence in Youth Mental Health, and Centre for Youth Mental Health, the University of Melbourne, Parkville, Australia (Nelson, Amminger, McGorry); Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Nieman); Specialized Early Psychosis Outpatient Service for Adolescents and Young Adults, Department of Psychiatry, Bruderholz, Switzerland. (Simon); Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan (Mizuno); Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea (T. Y. Lee, Kwon); Kwai Chung Hospital, New Territories, Hong Kong, People's Republic of China (Lam); Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom (Perez); Nyiro Gyula Hospital, National Institute of Psychiatry and Addictions, Budapest, Hungary (Keri); Centre for Social Psychiatry, Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Zurich, Switzerland (Metzler, Kawohl, Rössler); Department of General Psychiatry, Institute of Mental Health, Singapore, Singapore (J. Lee); Department of Psychiatry, Corporacio Sanitaria Parc Tauli Sabadell, Barcelona, Spain (Labad); Department of Clinical Child and Adolescent Studies, Leiden University, Leiden, the Netherlands (Ziermans); Department of Psychiatry, Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea (An); Department of Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan (Liu); Center for Psychiatric Research, Maine Medical Center, Portland, Maine (Woodberry); Departments of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Woodberry); Psychiatry Department, University Hospital Farhat Hached, Sousse, Tunisia (Braham); Department of Psychiatry, Columbia University, New York, New York (Corcoran); Institute of Brain, Behaviour and Mental Health, University of Manchester, and Greater Manchester West National Health Service Mental Health Foundation Trust, Manchester, United Kingdom (Yung).

Author Contributions: Dr Fusar-Poli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fusar-Poli, Cappucciati, McGuire.
Acquisition, analysis, or interpretation of data: Fusar-Poli, Cappucciati, Borgwardt, Woods, Addington, Nelson, Nieman, Stahl, Rutigliano, Riecher-Rössler, Simon, Mizuno, T. Y. Lee, Kwon, Perez, Keri, Amminger, Metzler, Kawohl, Rössler, J. Lee, Labad, Ziermans, An, Liu, Woodberry, Braham, Corcoran, McGorry, Yung, McGuire.
Drafting of the manuscript: Fusar-Poli, Cappucciati, Nelson, T. Y. Lee, Amminger, J. Lee, Braham, Yung.
Critical revision of the manuscript for important intellectual content: Fusar-Poli, Cappucciati, Borgwardt, Woods, Addington, Nelson, Nieman, Stahl, Rutigliano, Riecher-Rössler, Simon, Mizuno, T. Y. Lee, Kwon, Lam, Perez, Keri, Amminger, Metzler, Kawohl, Rössler, J. Lee, Labad, Ziermans, An, Liu, Woodberry, Corcoran, McGorry, Yung, McGuire.
Statistical analysis: Fusar-Poli, Cappucciati, Nelson, Nieman, Stahl, T. Y. Lee, Amminger, Metzler.
Obtained funding: Fusar-Poli, Addington, Riecher-Rössler, Simon, Rössler, J. Lee, Braham, Corcoran, McGuire.
Administrative, technical, or material support: Fusar-Poli, Addington, Riecher-Rössler, Simon, Lam, Perez, Keri, Kawohl, Rössler, J. Lee, McGuire.
Study supervision: Fusar-Poli, Borgwardt, Addington, Riecher-Rössler, T. Y. Lee, Kwon, Kawohl, Rössler, McGorry, McGuire.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by a 2014 NARSAD Young Investigator Award (Dr Fusar-Poli). The research leading to these results has also received funding from the European Community's Seventh Framework Programme under grant agreement HEALTH-F2-2013-603196 (Project PSYSCAN [Translating Neuroimaging Findings from Research into Clinical Practice]).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996;22(2):283-303.

2. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107-120.

3. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*. 2015;14(3):322-332.

4. Kempton MJ, Bonoldi I, Valmaggia L, McGuire P, Fusar-Poli P. Speed of psychosis progression in people at ultra high clinical risk: a complementary meta-analysis. *JAMA Psychiatry*. 2015;72(6):622-623.

5. Fusar-Poli P. The enduring search for Koplik spots of psychosis. *JAMA Psychiatry*. 2015;72(9):863-864.

6. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17(12):1174-1179.

7. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69(3):220-229.

8. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry*. 2013;70(8):793-802.

9. Fusar-Poli P, Radua J, Frascarelli M, et al. Evidence of reporting biases in voxel-based morphometry (VBM) studies of psychiatric and neurological disorders. *Hum Brain Mapp*. 2014;35(7):3052-3065.

10. Fusar-Poli P, Borgwardt S, Valmaggia L. Heterogeneity in the assessment of the at-risk mental state for psychosis. *Psychiatr Serv*. 2008;59(7):813.

11. Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? *Schizophr Res*. 2011;125(1):62-68.

12. Gross G, Huber G, Klosterkötter J, Linz M. *Bonn Scale for the Assessment of Basic Symptoms*. Berlin, Germany: Springer-Verlag; 1987.

13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.

14. Yung AR, Yuen HP, McGorry PD, Phillips L, Kelly D, Dell'Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At Risk Mental States (CAARMS). *Aust N Z J Psychiatry*. 2005;39:964-971.

15. McGlashan TH, Walsh B, Wood SJ. *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-up*. New York, NY: Oxford University Press; 2010.

16. Riecher-Rössler A, Aston J, Ventura J, et al. The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity. *Fortschr Neurol Psychiatr*. 2008;76(4):207-216.

17. Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. *Schizophrenia Proneness Instrument, Adult Version (SPI-A)*. Rome, Italy: Giovanni Fioriti Editore; 2007.

18. Schultze-Lutter F, Koch E. *Schizophrenia Proneness Instrument, Child and Youth Version (SPI-CY)*. Rome, Italy: Giovanni Fioriti Editore; 2010.

19. Klosterkötter JGG, Huber G, Wieneke A, Steinmeyer EM, Schultze-Lutter F. Evaluation of the Bonn Scale for the Assessment of Basic Symptoms—BSABS as an instrument for the assessment of schizophrenia proneness: a review of recent findings. *Neurol Psychiatry Brain Res*. 1997;5:137-150.

20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

21. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72(1):39.

22. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998;17(8):857-872.

23. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607-611.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

25. Harbord R, Higgins J. Metaregression in Stata. *Stata J*. 2008;8(4):493-519.

26. Borenstein M, Hedges L, Higgins J. *Introduction to Meta-analysis*. Hoboken, NY: John Wiley & Sons; 2009.

27. Lipsey M, Wilson D. *Practical Meta-analysis*. Thousand Oaks, CA: Sage Publications; 2000.

28. Steichen T. *Nonparametric Trim and Fill Analysis of Publication Bias in Meta-analysis*. Chicago, IL: StataCorp LP; 2001:10-57.

29. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*. 2008;61(10):991-996.

30. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323(7304):101-105.

31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

32. Harbord R, Harris R, Sterne A. Updated tests for small-study effects in meta-analyses. *Stat Med*. 2009;9(2):197-210.

33. Lee J, Rekhi G, Mitter N, et al. The Longitudinal Youth at Risk Study (LYRIKS)—an Asian UHR perspective. *Schizophr Res*. 2013;151(1-3):279-283.

34. Winton-Brown TT, Harvey SB, McGuire PK. The diagnostic significance of BLIPS (Brief Limited Intermittent Psychotic Symptoms) in psychosis. *Schizophr Res*. 2011;131(1-3):256-257.

35. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29(4):703-715.

36. Schultze-Lutter F, Schimmelmann BG, Ruhrmann S. The near Babylonian speech confusion in early detection of psychosis. *Schizophr Bull*. 2011;37(4):653-655.

37. Fusar-Poli P, Van Os J. Lost in transition: setting the psychosis threshold in prodromal research. *Acta Psychiatr Scand*. 2013;127(3):248-252.

38. Fusar-Poli P, Cappucciati M, Bonoldi I, et al. Meta-analytical prognosis of brief psychotic episodes: a momentary lapse of reason. *JAMA Psychiatry*. In press. doi:10.1001/jamapsychiatry.2015.2313.

39. Fusar-Poli P, Frascarelli M, Valmaggia L, et al. Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychol Med*. 2015;45(6):1327-1339.

40. Cornblatt BA, Carrión RE, Auther A, et al. Psychosis prevention: a modified clinical high risk perspective from the Recognition and Prevention (RAP) Program. *Am J Psychiatry*. 2015;172(10):986-994.

41. Kelleher I, Murtagh A, Molloy C, et al. Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. *Schizophr Bull*. 2012;38(2):239-246.

42. Debbané M, Eliez S, Badoud D, Conus P, Flückiger R, Schultze-Lutter F. Developing psychosis and its risk states through the lens of schizotypy. *Schizophr Bull*. 2015;41(suppl 2):S396-S407.

43. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull*. 2014;40(1):28-38.

44. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ*. 1995;311(7003):485.

45. Lenth R. Some practical guidelines for effective sample-size determination. *Am Stat*. 2001;55:187-193.

46. Hoenig J, Heisey D. The abuse of power: the pervasive fallacy of power calculations in data analysis. *Am Stat*. 2001;55:19-24.

47. Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy*. 2001;21(4):405-409.

48. Schultze-Lutter F, Klosterkötter J, Michel C, Winkler K, Ruhrmann S. Personality disorders and accentuations in at-risk persons with and without conversion to first-episode psychosis. *Early Interv Psychiatry*. 2012;6(4):389-398.

49. Fusar-Poli P, Meneghelli A, Valmaggia L, et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry*. 2009;194(2):181-182.

50. Fusar-Poli P, Rocchetti M, Sardella A, et al. Disorder, not just a state of risk: meta-analysis of functioning and quality of life in subjects at high clinical risk for psychosis. *Br J Psychiatry*. In press.

51. Wiltink S, Velthorst E, Nelson B, McGorry PM, Yung AR. Declining transition rates to psychosis: the contribution of potential changes in referral pathways to an ultra-high-risk service. *Early Interv Psychiatry*. 2015;9(3):200-206.

52. Yung AR, Yuen HP, Berger G, et al. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull*. 2007;33(3):673-681.

53. Fusar-Poli P, Schultze-Lutter F, Cappucciati M. The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. *Schizophr Bull*. 2015;(November):20.

54. Cornblatt BA, Lencz T, Smith CW, et al. Can antidepressants be used to treat the schizophrenia prodrome? results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry*. 2007;68(4):546-557.

55. van der Gaag M, Smit F, Bechdolf A, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res*. 2013;149(1-3):56-62.

56. Schultze-Lutter F, Michel C, Schmidt SJ, et al. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry*. 2015;30(3):405-416.

57. Fusar-Poli P, Bechdolf A, Taylor MJ, et al. At risk for schizophrenic or affective psychoses? a meta-analysis of *DSM/ICD* diagnostic outcomes in individuals at high clinical risk. *Schizophr Bull*. 2013;39(4):923-932.

58. Valmaggia LR, Byrne M, Day F, et al. Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase. *Br J Psychiatry*. 2015;207(2):130-134.

59. Buchy L, Cadenhead KS, Cannon TD, et al. Substance use in individuals at clinical high risk of psychosis. *Psychol Med*. 2015;45(11):2275-2284.

60. Modinos G, Allen P, Frascarelli M, et al. Are we really mapping psychosis risk? neuroanatomical signature of affective disorders in subjects at ultra high risk. *Psychol Med*. 2014;44(16):3491-3501.